(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 March 2003 (20.03.2003)

PCT

(10) International Publication Number
WO 03/022262 A1

(51) International Patent Classification[7]: A61K 31/205, 31/519, 31/4985, A61P 15/00, 15/10

(21) International Application Number: PCT/LV02/00004

(22) International Filing Date: 4 March 2002 (04.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P-01-00134 7 September 2001 (07.09.2001) LV

(71) Applicants and
(72) Inventors: **KALVINSH, Ivars** [LV/LV]; Libieshu 25, LV-5052 Ikshkile (LV). **VEVERIS, Maris** [LV/LV]; Vejavas 10/2, Apt. 20, LV- 1035 Riga (LV). **BIRMANS, Anatolijs** [LV/LV]; Hospitalu 8-35, LV- 1013 Riga (LV).

(74) Agent: **FOGEL, Abraham**; Alfa-Patents SIA, Viranes 2, LV- 1073 Riga (LV).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/022262 A1

(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING GAMMA-BUTYROBETAINE

(57) Abstract: New medical use for gamma-butyrobetaine is disclosed. Also disclosed are pharmaceutical compositions, containing gamma-butyrobetaine or combination thereof with 3-(2,2,2-trimethylhydrazinium)propionate or sildenafil for oral, parenteral, subcutaneous, transdermal, topical, sublingual, intrauretral, intranasal or rectal application, useful for stimulation of sexual activity and potency in mammals. The disclosed compositions, when applied orally for 6 weeks to non-narcotized male rats substantially increase their sexual activity, decreasing the arousal time, increasing the number of copulations and resultativeness of mounting attempts. When applied by intracavernous or intravenous route said pharmaceutical compositions increase intracorporeal pressure and duration of erection, as well as restore stimulation-induced reflectory erection in narcotized animals.

PHARMACEUTICAL COMPOSITION COMPRISING GAMMA-BUTYROBETAINE

Invention relates to a second medical use of a known pharmaceutical agent and composition comprising thereof, particularly to normalize and stimulate sexual activity and potency in mammals. The invention discloses novel effects of known substances, showing in combination unexpected level of pharmacological activity. In particular, a pharmaceutical composition is disclosed, comprising as active ingredients gamma-butyrobetaine (GBB) in combination with 3-(2,2,2-trimethylhydrazinium)propionate (THP) or phosphodiesterase inhibitor.

GBB (actinine), an intermediate in the synthesis of carnitine in mammalian organism, initially was characterised as a toxic substance, inducing tachypnea, salivation and lacrimation, mydriasis, vasoconstriction and cardiac arrest in diastole (Linneweh W. Z physiol Chem., 1929;**42**:181). Further research demonstrated that the toxicity of GBB is extremely low (LD_{50} = 7000 mg/kg subc.) (Rotzsch W, Lorenz I, Strack E. Acta biol med ger 1959;**3**:28-36). The cardiovascular effects of GBB were compared to that of acetylcholine (Hosein EA, McLennan H. Pharmacological action of gamma-butyrobetaine. Nature 1959;**183**:328), but later the data were renounced by the same author, who had in fact investigated the effects of the GBB methyl esther. Another investigators held, that GBB is pharmacologically inert (Hosein EA, Proulx P. Isolation and probable functions of betaine esters in brain metabolism. Nature 1960;**187**:321. Burgen ASV, Hobiger F. Brit J Pharmacol. 1949;**4**:229. Strack E, Foesterling K. Z physiol Chem. 1953;**295**:377). Contrary to that, radical scavenger properties (Akahira M, Hara A, Abiko Y. Effect of MET-88, a gamma-butyrobetaine hydroxylase inhibitor, on myocardial derangements induced by hydrogen peroxide in the isolated perfused rat heart. Fundam Clin Pharmacol. 1997;**11(4)**:356) and cardioprotective activity (Kalvins I, Veveris M. Latvian patent Nr. 11727) were later demonstrated for GBB. It was also disclosed, that pharmaceutical composition, comprising GBB as the active principle, is useful for treating of carnitine deficiency (Cavazza C. Pharmaceutical composition comprising gamma-butyrobetaine. UK Patent Application GB 2 091 101 (1982)). There are no data on the influence of GBB on sexual activity and potency of mammals.

3-(2,2,2-Trimethylhydrazinium)propionate (THP) is known also as a medicine Mildronate or Quaterine (UK patent 2105992). It interferes with carnitine biosynthesis and, consequently, limits the transporting of long-chain fatty acids through mitochondrial membranes (Simkhovich BZ, Shutenko ZV, Meirena DV et al. 3-(2,2,2-trimethylhydrazinium)propionate (THP) - a novel γ-

butyrobetaine inhibitor with cardioprotective properties. Biochem Pharmacol 1988;37:195). It has therefore found application as metabolic corrector in ischemic diseases of different origin and cytoprotector in hypoxic conditions.

A pharmaceutical composition for the treatment of cardiovascular diseases, containing 3-(2,2,2-trimethylhydrazinium)propionate and gamma-butyrobetaine was disclosed in Latvian patent LV 11728.

However, there are no data on the influence of 3-(2,2,2-trimethylhydrazinium)propionate (THP) or combinations thereof with other substances on sexual activity and potency of mammals.

We have surprisingly discovered that gamma-butyrobetaine and/or THP induce substantial and long-lasting increase of sexual activity in laboratory animals. Moreover, the combination of both substances produce a more prolonged and higher increase of the intracavernous pressure than each of the constituent substances separately. Moreover, GBB or combination thereof with THP, exert a positive influence on intracavernous pressure, induced by reflectory stimulation. Thus we have unexpectedly discovered that GBB or combination thereof with THP, are useful for stimulating of both the sexual activity and potency of mammals. This activity can not be attributed to the known effects of GBB and/or THP on the fatty acids turnover or other known physiological effects of said substances.

The pharmacological effects of GBB, THP and their combination on the sexual activity of mammals was investigated by a model based on rat copulating behaviour in state of physiological depression.

Experiments were conducted on adult Wistar rats of both sexes with initial body weight of 300 - 330 g. During the experiment, the animals were kept in standard crates in groups of 6. The feed was a standartized diet R70 (LABFOR, Lactamin AB, Sweden). The room temperature was kept at 21 - 23 °C, relative humidity at 65 ± 10%, 12 hour light/darkness cycle. During one week before the experiment it was established that the average water consumption by the rats was 8.2 - 12% (average - 10%) of their body mass.

Male rats were distributed randomly into 4 groups, each of 6 animals, and supplied for 6 weeks with the following aqueous solutions:

Group 1 (Control Group) - drinking water without any additives;

Group 2 (GBB Group) - drinking water was supplemented by gamma-butyrobetaine (0.015% by weight), resulting in the average daily gamma-butyrobetaine intake of 15 mg/kg;

Group 3 (THP Group) - drinking water was supplemented by THP (0.06% by weight), resulting in the average daily THP intake of 60 mg/kg;

Group 4 (GBB + THP Group) - drinking water was supplemented by THP (0.06% by weight) and gamma-butyrobetaine (0.015% by weight), resulting in the average daily THP intake of 60 mg/kg and gamma-butyrobetaine intake of 15 mg/kg.

The copulating activity of male rats was tested four times: after one week, after four weeks, after six weeks and 48 - 50 hours after the discontinuation of substance intake, when all animals were receiving drinking water without additives.

The tests were conducted between 10 and 12 a.m. 6 male rats of one group were placed into a clean, well illuminated crate (box). After 5 min. adaptation period 2 female rats were placed into the box for 10 minutes. For each male rat the following data were collected:

1) copulating intensity (number of copulations during the exposition period);
2) arousal period, with separate registration of the delay time - the period until the male rat displays interest in female rat, and number of approaching/mounting attempts during the exposition period;
3) postcoital period - the behaviour of male rats during 5 min. period after the removal of females. The postcoital behaviour was characterized by following marks: 0 - the animal is passive, lays down; 1 - the rat is quiet, grooming; 2 - the rat is mobile, rutting; 3 - the animal is active, aggressive.

The female rats used were in the estrus phase, induced by i.p. injection of 0.2 ml 0.1% estradiol dipropionate 48 h before the test.

There were no substantial changes in water consumption attributable to experimental substances, while the sexual behaviour of rats in experimental groups was substantially different from that of control group.

Already a week after the start of the experiment, animals receiving GBB or GBB+THP displayed substantially higher sexual interest and activity in sexual contacts, as well as longer postcoital agitation period. The continuing application of GBB resulted in increase of sexual activity, reflected in higher copulation intensity, while rutting and general activity of animals was relatively less influenced (Tables 1 - 4).

Table 1. **The influence of therapeutic agents on the number of mounting attempts of male rats**

Duration of therapy	1 week	4 weeks	6 weeks	Post-therapy
Control	1.8±0.8	2.2±0.5	2.3±0.5	2.7±0.5
GBB	**3.8*±0.4**	3.7±0.7	3.3±0.6	3.2±0.5
THP	2.7±0.6	3.0±0.7	3.7±0.5	3.4±0.7
THP+GBB	**3.8*±0.4**	**4.0*±0.4**	3.7±0.5	**4.2*±0.4**

*) $p<0.05$ v.s. control

Table 2. **The influence of therapeutic agents on the delay time before attempts of mounting (min)**

Duration of therapy	1 week	4 weeks	6 weeks	Post-therapy
Control	5.8±1.4	3.8±0.8	4.7±1.1	3.5±0.7
GBB	3.7±0.9	**1.8*±0.4**	2.8±0.9	2.6±0.6
THP	5.3±1.0	2.1±0.5	2.3±0.5	2.4±0.7
THP+GBB	3.5±0.6	**1.6*±0.4**	**1.8*±0.4**	**1.7*±0.4**

*) $p<0.05$ v.s. control

Table 3. **The influence of therapeutic agents on the number of copulations**

Duration of therapy	1 week	4 weeks	6 weeks	Post-therapy
Control	0.3±0.3	0.5±0.3	0.5±0.2	0.5±0.2
GBB	0.8±0.3	1.3±0.5	**1.2*±0.2**	0.7±0.2
THP	0.5±0.3	1.2±0.4	0.8±0.3	1.0±0.3
THP+GBB	0.8±0.3	**1.8*±0.4**	1.5±0.4	**1.2*±0.2**

*) $p<0.05$ v.s. control

Table 4. **The influence of therapeutic agents on rat post-coital agitation period**

Duration of therapy	1 week	4 weeks	6 weeks	Post-therapy
Control	0.8±0.3	1.0±0.4	1.2±0.3	1.5±0.4
GBB	**2.0*±0.4**	1.2±0.3	1.5±0.4	1.2±0.3
THP	1.0±0.4	1.4±0.5	1.8±0.3	1.2±0.4
THP+GBB	**2.0*±0.4**	1.4±0.5	1.7±0.3	1.8±0.4

*) $p<0.05$ v.s. control

The combined use of GBB and THP resulted in hightened sexual interest and copulating activity during all experimental period. After the discontinuing of medication, only the GBB + THP Group displayed higher copulating activity compared with controls.

Thus we have experimentally demonstrated, that GBB alone and in combination with THP after 6 week treatment period produces a substantial and lasting increase of copulating activity in male rats. Moreover, we found a surprising increase of efficiency for the combination of two substances as compared to their activity when used separately.

In further experiments the novel compositions were compared with a known potency stimulator papaverine (Sarosdy MF, Hudnall CH, Erickson DR, Hardin TC, Novicki DE. A prospective double-blind trial of intracorporeal papaverine versus prostaglandin E1 in treatment of impotence. J Urol, 1989;**141**:551), which is an efficient erection stimulant at intracorporeal injection.

Adult male rats, weighing 300 - 410 g were used. The influence of the experimental substances on the penile erection was evaluated using the experimental model, where changes of intracorporeal pressure was measured (Chen KK et al. J Urol, 1992;**147**:1124).

Rats were anesthetized by sodium pentobarbital (50 mg/kg i.p. plus additionally 8 mg/kg/h i.v.). Body temperature was kept at 37 - 37.4 °C (rectal control) by heating lamp. Endotracheal tube was inserted to assure adequate respiration under anesthesia. Number 25 needle filled with heparinized saline was connected to pressure transducer and introduced into corpus cavernosum penis. Intracavernous pressure and II standard lead on an ECG was continuously recorded on physiograph DMP-4B (Narco Bio-Systems, USA). In some experiments arterial pressure in common carotid artery was also recorded. The effects of experimental substances were determined both at intravenous and intracavernous introduction route. For the intracorporeal injection the substances were dissolved in isotonic (0.9%) NaCl solution and the dose introduced in 0.05 ml of liquid. Papaverine hydrochloride, used in clinics for potency testing, served as the positive standard (intracavernous injection 0.2 mg per rat; intravenously 2.0 mg/kg). Gamma-butyrobetaine (GBB) was introduced separately and in combination with THP or phosphodiesterase inhibitor, in particular, sildenafil.

Gamma-butyrobetaine (GBB) (intracavernous injection 0.02 – 0.1 mg per rat, usually 0.05 mg per rat; intravenously 2.0 mg/kg) and THP (intracavernous injection 0.2 mg per rat; intravenously 10.0 mg/kg) were introduced separately and as combination (GBB+THP).

Sildenafil (intracavernous injection 0.15 mg per rat, intravenously 3.0 mg/kg) was introduced separately and in combination (GBB + sildenafil).

It was discovered that intracavernous injection of GBB produces a pronounced dose-dependent, but relatively short-termed increase of intracorporeal pressure (Table 5).

***Table 5.* Influence of intracavernous injections of therapeutic agents on intracorporeal pressure in narcotized rats**

Therapeutic agent	Dose	Increase of intracorporeal pressure		Duration of effect
	mg	mmHg	% of papaverine***	min
GBB	0.02	**11.25**±3.3**	30.6	**3.0*±0.7**
GBB	0.05	31.5±5.1	85.7	**4.3*±0.9**
THP	0.2	**2.7**±1.5**	7.3	**0.8**±0.4**
THP + GBB	0.2+0.05	40.0±5.6	108.8	10.4±2.0
Sildenafil	0.15	38.5±7.3	104.8	7.5±2.7
Sildenafil + GBB	0.15+0.05	35.2±8.4	95.8	**17.6*±4.3**
Papaverine	0.2	36.75±4.1	100	8.8±1.4

*) $p<0.05$ v.s. papaverine. **) $p<0.01$ v.s. papaverine.

***) in % of the increase produced by papaverine

THP did not produce significant changes of intracorporeal pressure. The activity of GBB in this test was also inferior to that of papaverine. Surprisingly, the effect of the combination of GBB with THP or sildenafil was equal or superior to that of papaverine. Both the effect produced by the combination, and its duration was superior to that induced by each of the ingredients separately.

Since the intracavernous injection is not popular due to inconvenience to patient, intravenous route was selected for further evaluation.

It was demonstrated that intravenous papaverine and THP display little effect on intracorporeal pressure, while GBB and GBB-THP composition are highly efficient in increasing the intracorporeal pressure (Table 6).

It is important to notice, that the GBB-THP in combination and GBB plus sildenafil sustains its effect 2.25 times or even, correspondingly, 5.46 times longer than the GBB alone. It is also essential to note that only GBB-THP in combination induced a pronounced positive response to reflex penis stimulation resulting in increase of intracorporeal pressure, a response untypical for narcotized animals.

Table 6. **Influence of intravenous injections of therapeutic agents on intracavernous pressure in narcotized rats**

Agent	GBB	THP	THP+GBB	Sildenafil	Sildenafil+GBB	Papaverine
Reflectory increase of intracavernous pressure (mm Hg)	7.3*±2.0	2.7±1.2	21.7*±10.4	11.8*±3.6	7.3*±2.1	0.3±0.3
Changes of intracavernous pressure (mm Hg)	22.0*±3.6	1.3±0.9	29.7**±4.3	12.3*±4.8	28.4*±7.9	0.6±0.6
Duration of effect (min)	2.8±0.7	0.9±0.5	6.3**±1.9	2.5±1.1	15.3*±4.2	0.9±0.9

*) $p<0.05$ v.s. papaverine

**) $p<0.01$ v.s. papaverine

Thus it was demonstrated, that pharmaceutical compositions containing GBB or combination thereof with THP or sildenafil produced an increase of intracorporeal pressure not only at intracavernous injection, but also, contrary to papaverine, at intravenous route. We demonstrated the surprising efficiency of the composition comprising the combination of GBB and THP and GBB plus sildenafil in inducing the rise of intracorporeal pressure and the unexpected sustained duration of effect, compared to that of each component of the combination used alone, as well as restoration of positive reflex response to mechanical penis stimulation.

Considering the positive effects the substances displayed orally, they are useful for stimulation of sexual activity and erection both at norm and at physiological depression of erectile function, being introduced both enterally and parenterally.

In cases when the active ingredients are administered parenterally by injections or orally as drops, syrup or beverage, the pharmaceutical composition contains the combination of gamma-butyrobetaine with THP or gamma-butyrobetaine with sildenafil in the summary amount of 0.5-40% by total weight of pharmaceutical form and distilled water, physiologic saline solution, glucose solution, or buffer solution as a pharmaceutically acceptable solvent.

In cases when the combination of active ingredients is administered as tablets, caplets, capsules, pills, granules, or powders, the pharmaceutical composition contains the combination of gamma-butyrobetaine with THP or gamma-butyrobetaine with sildenafil in the summary amount of 0.5 to 5 g by weight per tablet, caplet, capsule, pill, granule, or powder dosage unit.

In cases when the active ingredients are administered transcutaneously, topically, sublingually, intrauretrally or intranasally their content is 0.5-40% by total weight of pharmaceutical form.

The pharmacutical composition, in addition, may include other pharmacutical agents, such, as for example, other phosphodiesterase type V inhibitors (vardenafil, tadalafil and related).

Claim.

1. Use of gamma-butyrobetaine as free base or pharmaceutically acceptable salt in the production of a medicament for normalizing and stimulating of sexual activity and potency in mammals.

2. A pharmaceutical composition for stimulation of sexual activity and potency in mammals comprising gamma-butyrobetaine in association with pharmaceutically acceptable diluent or carrier.

3. The parmaceutical composition of Claim 2 further comprising 3-(2,2,2-trimethylhydrazinium)-propionate as free base or pharmaceutically acceptable salt.

4. The pharmaceutical composition of Claim 2 further comprising a phosphodiesterase inhibitor.

5. The pharmaceutical composition of Claim 4 wherein the phosphodiesterase inhibitor is type V inhibitor.

6. The pharmaceutical composition of Claim 5 wherein the phosphodiesterase inhibitor of type V is selected from the group consisting of sildenafil, vardenafil, tadalafil and related.

7. Use of the pharmaceutical composition of any of Claims 2 to 6 in the production of a medicament for normalizing and stimulating of sexual activity and potency in mammals.

INTERNATIONAL SEARCH REPORT

ational Application No
PCT/LV 02/00004

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/205 A61K31/519 A61K31/4985 A61P15/00 A61P15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EMBASE, SCISEARCH, MEDLINE, BIOSIS, WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 06795 A (KALVINSH IVARS ;VEVERIS MARIS (LV)) 27 February 1997 (1997-02-27) claims 1-10	2
X	US 4 382 092 A (CAVAZZA CLAUDIO) 3 May 1983 (1983-05-03) claims 1,2	2
X	WO 97 06794 A (KALVINSH IVARS ;VEVERIS MARIS (LV)) 27 February 1997 (1997-02-27) claims 1-10	2,3

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2002	14/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	van der Kooij, M

Continuation of Box I.2

Present claims 4 and 5 relate to a compound defined by reference to a desirable characteristic or property, namely "phosphodiesterase inhibitory" activity or "phosphodiesterase type V inhibitory" activity. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the specific phosphodiesterase type V inhibitors mentioned in claim 6, i.e. sildenafil, vardenafil and tadalafil in combination with gamma-butyrobetaine in relation to normalizing and stimulating the sexual activity and potency of mammals with due regard to the general idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9706795 A	27-02-1997	LV 11727 A	20-04-1997
		LV 11727 B	20-08-1997
		WO 9706795 A1	27-02-1997
US 4382092 A	03-05-1983	IT 1198434 B	21-12-1988
		AU 548787 B2	02-01-1986
		AU 7908781 A	15-07-1982
		BE 891639 A1	16-04-1982
		CH 649218 A5	15-05-1985
		DE 3200016 A1	12-08-1982
		FR 2497510 A1	09-07-1982
		GB 2091101 A ,B	28-07-1982
		GR 75132 A1	13-07-1984
		IE 52404 B1	14-10-1987
		JP 1738989 C	26-02-1993
		JP 4024325 B	24-04-1992
		JP 57136516 A	23-08-1982
		LU 83869 A1	07-05-1982
		NL 8200022 A	02-08-1982
		SE 453569 B	15-02-1988
		SE 8200007 A	07-07-1982
WO 9706794 A	27-02-1997	LV 11728 A	20-04-1997
		CA 2229228 A1	27-02-1997
		EP 0845986 A1	10-06-1998
		JP 10512286 T	24-11-1998
		JP 3072858 B2	07-08-2000
		LV 11728 B	20-08-1997
		WO 9706794 A1	27-02-1997
		US 5859056 A	12-01-1999